Remarks

The present invention provides compositions containing second or third generation antidepressants, such as those formulated for topical application, or for injection in slow release delivery vehicles. Invention compositions have been shown to produce analgesia in subjects having a site of local discomfort. Invention formulations possess the advantage of providing a higher and more efficacious concentration of the antidepressant to the region of the sensory nerve terminal than is achievable with systemic administration of the antidepressant. In addition, invention compositions for local administration greatly reduce the side effects that may result from systemic administration of antidepressants.

Claims 26-53 and 63-71 were pending before this communication. By this response, claims 26, 42, 43 and 53 have been amended to define the Applicants' invention with greater particularity. In addition, the title of the specification has been amended to reflect the subject matter of the present application. These amendments add no new matter as they are fully supported by the specification and the original claims. Attached hereto is a marked-up version of the changes made to the specification and the claims, labeled APPENDIX A.

By the present communication, claims 27-36, 45-48 and 63-71 have been cancelled without prejudice. Accordingly, claims 26, 37-44 and 49-53 are currently pending. For the Examiner's convenience, a clean copy of these claims is also provided in APPENDIX B.

The rejection of claims 63-71 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite, is respectfully traversed and has been rendered moot by the present communication. All of claims 63-71 have been cancelled by the present communication. Accordingly, reconsideration and withdrawal of this rejection under 35 U.S.C. § 112, second paragraph, are respectfully requested.

The rejection of claims 63-71 under 35 U.S.C. § 101, as allegedly being improper process claims, is respectfully traversed and has been rendered moot by the present communication. All

of claims 63-71 have been cancelled by the present communication. Accordingly, reconsideration and withdrawal of this rejection under 35 U.S.C. § 101, are respectfully requested.

The rejection of claims 26-29, 31-36, 42-46 and 48-50 under 35 U.S.C. § 102(b), as allegedly being anticipated by US Patent No. 4,395,420 to Bernstein ("Bernstein"), is respectfully traversed. Applicants' invention, as defined by amended claim 26 (and claims dependent thereon, i.e., claims 42-44, 49 and 50), distinguishes over Berstein by requiring compositions of heterocyclic antidepressants (i.e., second or third generation antidepressants), said compositions being useful for achieving local pain relief. Bernstein does not disclose or suggest compositions comprising heterocyclic antidepressants.

In contrast, as acknowledged by the Examiner, Bernstein "teaches topical tricyclic antidepressant compositions for treating pruritis" (emphasis added, Office Action, Paper No. 10, at page 4, paragraph 11). Specifically, Bernstein only discloses the use of doxepin, amitriptyline and imipramine (all tricyclic antidepressants) for treating pruritis. Accordingly, reconsideration and withdrawal of this rejection under 35 U.S.C. § 102(b) are respectfully requested.

The rejection of claims 26-29, 31-36, 42-46 and 48-50 under 35 U.S.C. § 102(b), as allegedly being anticipated by WO 97/10815 ("Frome"), is respectfully traversed. Applicants' invention, as defined by amended claim 26 (and claims dependent thereon, i.e., claims 42-44, 49 and 50), distinguishes over Frome by requiring compositions of heterocyclic antidepressants (i.e., second or third generation antidepressants), said compositions being useful for achieving local pain relief. Frome does not disclose or suggest compositions comprising heterocyclic antidepressants.

In contrast, as acknowledged by the Examiner, Frome "discloses topical tricyclic antidepressant compositions . . ." (emphasis added, Office Action, Paper No. 10, at page 3, paragraph 7). Specifically, Frome only discloses the use of one antidepressant, amitriptyline (a tricyclic antidepressant), for treating sympathetically mediated pain. Accordingly,

reconsideration and withdrawal of this rejection under 35 U.S.C. § 102(b) are respectfully requested.

The rejection of claims 26-29, 31-47 and 49-53 under 35 U.S.C. § 102(b), as allegedly being anticipated by US Patent No. 5,486,362 to Kitchel et al. ("Kitchel"), is respectfully traversed. Applicants' invention, as defined by amended claim 26 (and claims dependent thereon, i.e., claims 42-44 and 49-53), distinguishes over Kitchel by requiring compositions of heterocyclic antidepressants (i.e., second or third generation antidepressants), said compositions being useful for achieving local pain relief. Kitchel does not disclose or suggest compositions comprising heterocyclic antidepressants.

In contrast, as acknowledged by the Examiner, Kitchel "discloses topical controlled released microsphere compositions comprising tricyclic antidepressants" (emphasis added, Office Action, Paper No. 10, at page 3, paragraph 8). Specifically, Kitchel only discloses the use of one antidepressant, desipramine (a tricyclic antidepressant), for treating drug dependency. Accordingly, reconsideration and withdrawal of this rejection under 35 U.S.C. § 102(b) are respectfully requested.

The rejection of claims 26-51 under 35 U.S.C. § 102(e), as allegedly being anticipated by US Patent No. 5,922,341 to Smith and Place ("Smith") is respectfully traversed. As established by the declaration under 37 C.F.R. §1.131 submitted herewith, Smith is not a prior art reference under 35 U.S.C. § 102(e) with respect to the present claims. The submitted declaration documents the completion of the present invention prior to the effective date of Smith, the filing date of October 28, 1997. Applicants attest that the invention being claimed was actually reduced to practice in Canada, a NAFTA country, prior to October 28, 1997, but not before December 8, 1993. Therefore, Applicants respectfully submit that Smith is not a prior art reference under 35 U.S.C. § 102(e). Accordingly, reconsideration and withdrawal of this rejection under 35 U.S.C. § 102(e) are respectfully requested.

The rejection of claims 26-36 and 42-50 under 35 U.S.C. § 103(a), as allegedly being unpatentable over Bernstein or Frome, is respectfully traversed. Applicants invention, as defined by amended claim 26 (and claims dependent thereon, i.e., claims 42-44, 49 and 50), distinguishes over the art by requiring compositions of heterocyclic antidepressants (i.e., second or third generation antidepressants), said compositions being useful for achieving local pain relief.

As noted above, neither Bernstein nor Frome discloses compositions comprising second or third generation antidepressants. Neither reference even suggests the use of second or third generation antidepressants. One of skill in the art would not be motivated to substitute a second or third generation antidepressant for the tricyclic antidepressant in the compositions of these references because the second and third generation antidepressants were specifically developed to have distinct pharmacological properties from the tricyclic antidepressants previously known in the art.

In addition, second and third generation antidepressants are routinely orally administered. Moreover, such drugs are prescribed for indications distinct from local pain relief. For example, exemplary second and third generation antidepressants include venlafaxine and bupropion (see specification at page 19, lines 12-14). Venlafaxine hydrochloride (marketed as EFFEXOR) is indicated for the treatment of depression and is formulated as tablets for oral administration (Physicians Desk Reference monograph enclosed). Bupropion hydrochloride (marketed as WELLBUTRIN) is indicated for the treatment of depression and is formulated as tablets for oral administration (Physicians Desk Reference monograph enclosed); and is also marketed as ZYBAN as an aid to smoking cessation, also formulated as tablets for oral administration (Physicians Desk Reference monograph enclosed). Therefore, it would not have been obvious to one skilled in the art to formulate second or third generation antidepressants in a topical vehicle for pain relief. Accordingly, reconsideration and withdrawal of this rejection under 35 U.S.C. § 103(a) are respectfully requested.

The rejection of claims 26-36 and 42-53 under 35 U.S.C. § 103(a), as allegedly being unpatentable over Kitchel, is respectfully traversed. Applicants invention, as defined by

amended claim 26 (and claims dependent thereon, i.e., claims 42-44 and 49-53), distinguishes over the art by requiring compositions of heterocyclic antidepressants (i.e., second or third generation antidepressants), said compositions being useful for achieving local pain relief.

As noted previously, Kitchel does not disclose compositions comprising second or third generation antidepressants. Kitchel does not even suggest the use of second or third generation antidepressants. One of skill in the art would not be motivated to substitute a second or third generation antidepressant for the tricyclic antidepressant in the compositions of this reference for the reasons presented above. Therefore, it would not have been obvious to one skilled in the art to formulate second or third generation antidepressants in a topical vehicle for pain relief. Accordingly, reconsideration and withdrawal of this rejection under 35 U.S.C. § 103(a) are respectfully requested.

The rejection of claims 26-51 under 35 U.S.C. § 103(a), as allegedly being unpatentable over Smith is respectfully traversed. Applicants respectfully submit that Smith is not a prior art reference under 35 U.S.C. § 102(e) (see declaration under 37 C.F.R. § 1.131 discussed above). Thus, Applicants respectfully submit that Smith is not a proper prior art reference to establish a prima facie case of obviousness. Accordingly, reconsideration and withdrawal of this rejection under 35 U.S.C. § 103(a) are respectfully requested.

Conclusion

In view of the above amendment and remarks, reconsideration and favorable action on all claims are respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

Date: February 11, 2002

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Registration No. 31,192
Telephone: (858) 847-6711
Facsimile: (858) 792-6773

Foley & Lardner
P.O. Box 80278
San Diego, CA 92138-0278

Enclosures: **Appendices A and B**
Declaration under 37 C.F.R. § 1.131 with supporting exhibits (13 pages)
PDR mongraphs (6 pages)

APPENDIX A – ALTERED SPECIFICATION AND CLAIMS
VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification:

The title of the specification has been amended as follows:

-- [~~USE OF TRICYCLIC~~] ANTIDEPRESSANT[~~S~~] COMPOSITIONS USEFUL FOR LOCAL ANALGESIA --

In the claims:

Claims 26, 42, 43 and 53 have been amended as follows:

26. (Amended) A composition for local administration comprising a **second or third generation** [~~tricyclic or heterocyclic~~] antidepressant [~~other than doxepine~~], and a vehicle suitable for topical administration.

42. (Amended) The composition of claim **26** [~~23~~] further comprising an inert carrier.

43. (Amended) The composition of claim 42 wherein the inert carrier is selected from the group consisting of water, isopropyl alcohol, gaseous fluorocarbons, ethyl alcohol, polyvinyl pyrrolidone, propylene glycol, a fragrance, a gel-producing material, stearyl alcohol, stearic acid, spermaceti, sorbitan monooleate, methylcellulose, and suitable combinations **of any two or more** thereof.

53. (Amended) The composition according to claim 52 wherein the delivery vehicle is selected from **the group consisting of** a liposome, a microcapsule, **and** a polymer stabilized crystal.

Claims 27-36, 45-48 and 63-71 have been cancelled without prejudice.

9. Prior to October 28, 1997, experiments summarized in Appendix B demonstrate that the local administration of amitriptyline at 100 nmol reduces pain responses in rats simultaneously administered 2.5 % formalin. Two groups of rats (control = formalin and test = formalin + amitriptyline) were monitored for 60 minutes post-injection. Appendix B, page 1 shows the data sets of the number of flinches observed. Appendix B, page 2 shows the data sets of the time spent biting/liking. Appendix B, page 3 is a graphical representation of these data sets, demonstrating the reduction in both the number of flinches and the time spent biting/licking in the amitriptyline test group.

10. Prior to October 28, 1997, experiments summarized in Appendix C demonstrate that the local administration of amitriptyline at 10-100 nmol reduces pain responses in rats simultaneously administered 2.5 % formalin in a dose-dependent manner. Four groups of rats (control = formalin and test = formalin + amitriptyline at three different doses) were monitored for 60 minutes post-injection. Appendix C, page 1 shows the data sets of the number of flinches observed. Appendix C, page 2 shows the data sets of the time spent biting/liking. Appendix C, page 3 is a graphical representation of these data sets, demonstrating the dose-dependent reduction in both the number of flinches and the time spent biting/licking in the amitriptyline test groups.

11. The experiments summarized in Appendices A-C evidence completion of the present invention prior to October 28, 1997.

12. We each individually further declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent resulting therefrom.

Jan 21/2002
Date

Jana Sawynok

January 26/2002
Date

Mike Esser

Jan 21/02
Date

Allison Reid

t-test

APPENDIX A

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FORMALIN 0.75% i.d. + AMITRIPTYLINE 100nmol i.d. (COINJECTED) (#FLINCHES)

FORMALIN 0.75%

{/ File;CopyRange}b43..q43~

FORMALIN 0.75%

RAT # \ BIN	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	AUC 0-12	AUC 16-36	AUC 40-60	AUC 16-60	AUC 0-60
9713.13	0	2	1	8	9	20	19	16	16	8	9	2	5	0	1	3	88	25	113	116
9713.16	4	0	0	3	1	9	7	7	26	11	4	4	8	0	2	4	53	29	82	86
9713.17	0	0	0	6	6	16	8	13	16	14	8	9	3	1	4	0	65	39	104	104
9713.20	4	0	0	1	0	4	8	4	3	6	5	11	5	1	5	4	20	33	53	57
9713.21	0	0	0	0	6	4	14	15	3	1	4	8	2	2	3	0	42	20	62	62
9713.24	1	0	0	7	28	25	32	13	18	8	2	3	1	4	4	1	123	22	145	146
MEAN	1.5	0.3	0.2	4.2	8.3	13.0	14.7	11.3	13.7	8.0	5.3	6.2	4.0	1.3	3.2	2.0	65.2	28.0	93.2	95.2
N	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0
SD	2.0	0.8	0.4	3.3	10.2	8.7	9.7	4.8	9.0	4.4	2.7	3.7	2.5	1.5	1.5	1.9	36.3	7.2	34.4	33.9
SE	0.8	0.3	0.2	1.4	4.2	3.6	3.9	1.9	3.7	1.8	1.1	1.5	1.0	0.6	0.6	0.8	14.8	2.9	14.0	13.8

FORMALIN 0.75% i.d. + AMITRIPTYLINE 100nmol i.d. (COINJECTED)

RAT # \ BIN	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	AUC 0-12	AUC 16-36	AUC 40-60	AUC 16-60	AUC 0-60
9713.14	0	0	2	0	0	0	3	4	2	0	2	4	5	0	0	2	9	11	20	22
9713.15	0	0	1	0	5	4	14	1	5	6	2	10	5	0	0	1	29	23	52	53
9713.18	0	2	0	0	5	5	23	19	5	3	7	12	2	3	1	2	57	28	85	87
9713.19	0	0	0	0	1	0	0	3	0	1	4	4	2	5	2	0	4	18	22	22
9713.22	0	2	0	1	1	3	4	1	1	7	1	1	1	2	0	2	11	12	23	25
9713.23	0	0	0	0	2	2	6	9	3	1	7	4	0	2	4	0	22	18	40	40
MEAN	0.0	0.7	0.5	0.2	2.3	2.3	8.3	6.2	2.7	3.0	3.8	5.8	2.5	2.0	1.2	1.2	22.0	18.3	40.3	41.5
N	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0
SD	0.0	1.0	0.8	0.4	2.2	2.1	8.6	6.9	2.1	2.9	2.6	4.2	2.1	1.9	1.6	1.0	19.4	6.5	25.2	25.4
SE	0.0	0.4	0.3	0.2	0.9	0.8	3.5	2.8	0.8	1.2	1.1	1.7	0.8	0.8	0.7	0.4	7.9	2.6	10.3	10.4
																NS	2.05	2.05	2.05	2.05

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FORMALIN 0.75% i.d. + AMITRIPTYLINE 100nmol i.d. (COINJECTED) (TIME SPENT BITNG/LICKING)

FORMALIN 0.75%

{/ File;CopyRange}b43..q43~

FORMALIN 0.75%

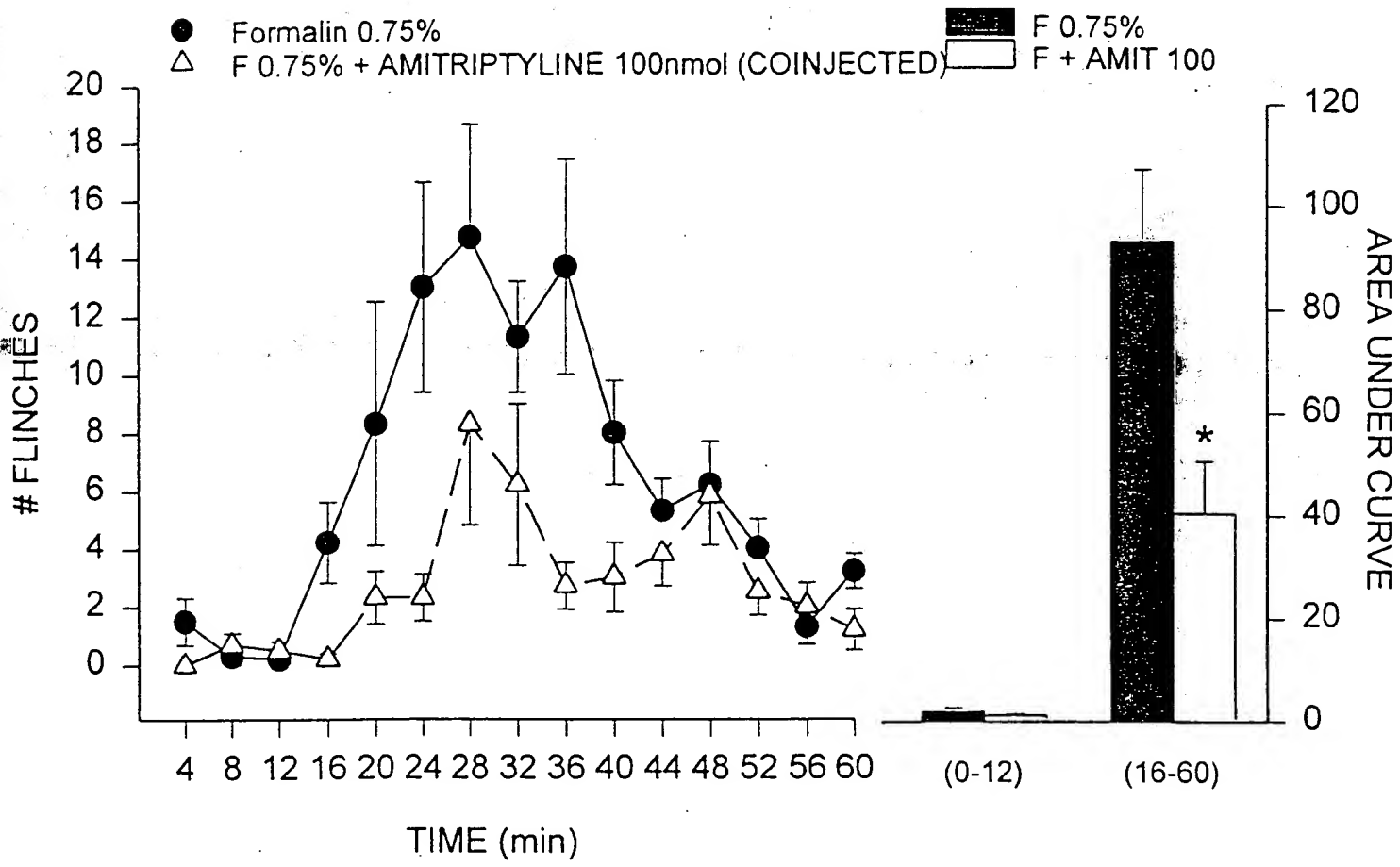
RAT # \ BIN	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	AUC 0-12	AUC 16-36	AUC 40-60	AUC 16-60	AUC 0-60
9713.13	0	0	0	0	0	0	26	0	0	0	40	0	1	0	0	0	26	41	67	67
9713.16	0	3	0	0	41	0	55	3	9	0	0	1	1	0	0	3	108	2	110	113
9713.17	0	0	0	0	0	26	0	13	0	0	0	0	0	0	0	0	39	0	39	39
9713.20	0	0	0	1	1	0	0	0	0	0	0	2	0	0	0	0	2	2	4	4
9713.21	0	0	0	0	0	0	0	19	0	0	0	0	0	0	0	0	19	0	19	19
9713.24	0	0	0	0	21	0	24	54	0	0	0	3	0	0	0	0	99	3	102	102
MEAN	0.0	0.5	0.0	0.2	10.5	4.3	17.5	14.8	1.5	0.0	6.7	1.0	0.3	0.0	0.0	0.5	48.8	8.0	56.8	57.3
N	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0
SD	0.0	1.2	0.0	0.4	17.1	10.6	22.1	20.7	3.7	0.0	16.3	1.3	0.5	0.0	0.0	1.2	44.1	16.2	43.6	44.4
SE	0.0	0.5	0.0	0.2	7.0	4.3	9.0	8.4	1.5	0.0	6.7	0.5	0.2	0.0	0.0	0.5	18.0	6.6	17.8	18.1

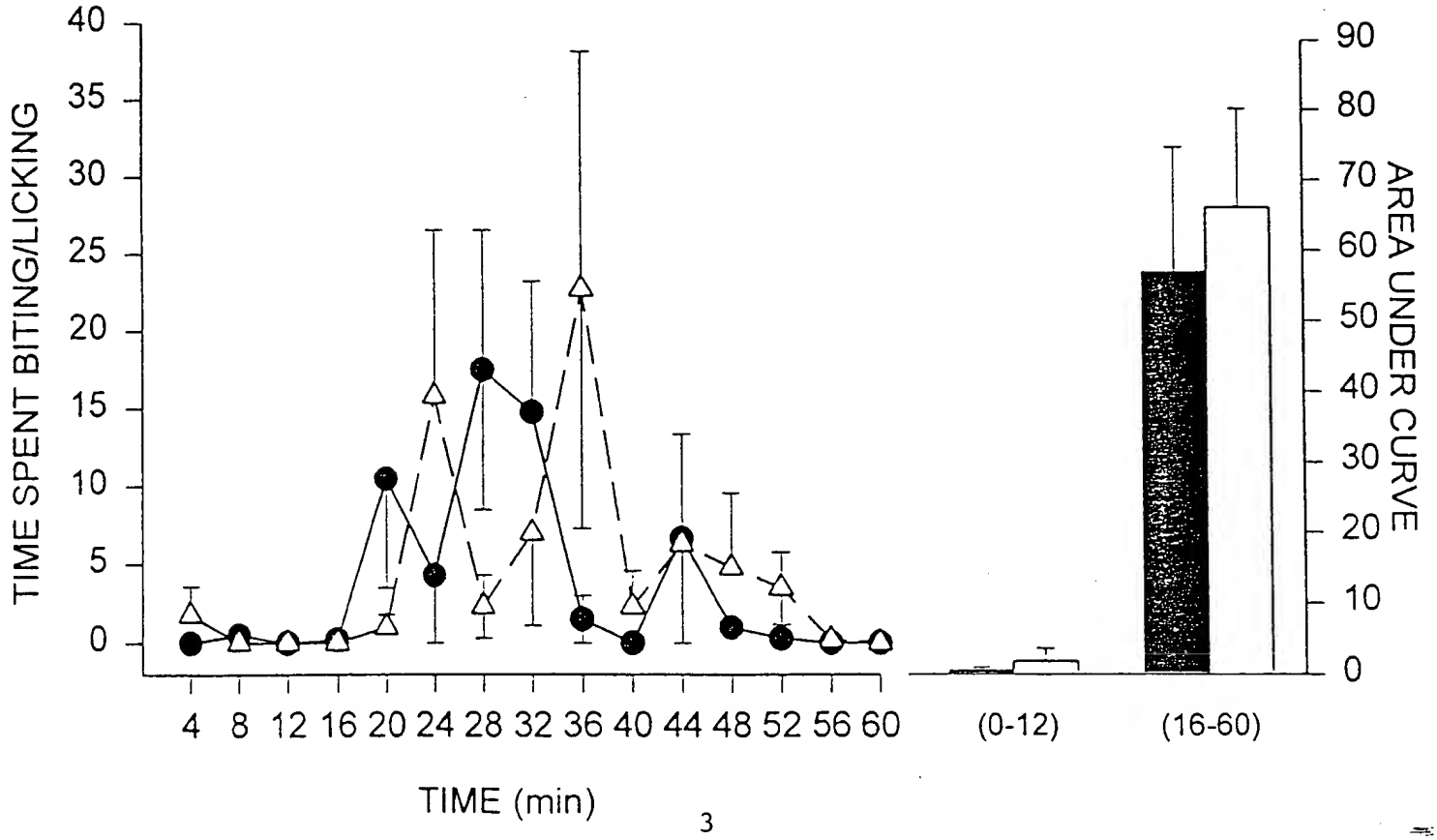
FORMALIN 0.75% i.d. + AMITRIPTYLINE 100nmol i.d. (COINJECTED)

RAT # \ BIN	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	AUC 0-12	AUC 16-36	AUC 40-60	AUC 16-60	AUC 0-60
9713.14	0	0	0	0	0	0	0	6	41	0	0	0	8	0	0	0	47	8	55	55
9713.15	0	0	0	0	0	0	0	0	0	0	38	29	13	0	0	0	0	80	80	80
9713.18	0	0	0	0	0	62	12	0	0	0	0	0	0	0	0	0	74	0	74	74
9713.19	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	1	1	2	2
9713.22	11	0	0	0	0	33	0	36	3	14	0	0	0	0	0	11	72	14	86	97
9713.23	0	0	0	0	5	0	2	0	92	0	0	0	0	0	0	0	99	0	99	99
MEAN	1.8	0.0	0.0	0.0	1.0	15.8	2.3	7.0	22.7	2.3	6.3	4.8	3.5	0.2	0.0	1.8	48.8	17.2	66.0	67.8
N	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0
SD	4.5	0.0	0.0	0.0	2.0	26.2	4.8	14.4	37.6	5.7	15.5	11.8	5.6	0.4	0.0	4.5	40.9	31.3	34.5	36.1
SE	1.8	0.0	0.0	0.0	0.8	10.7	2.0	5.9	15.4	2.3	6.3	4.8	2.3	0.2	0.0	1.8	16.7	12.8	14.1	14.7

Group 9713-1B

FORMALIN 0.75% + AMITRIPTYLINE 100nmol (COINJECTED)





APPENDIX B

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FORMALIN 2.5% + AMITRIPTYLINE 100nmol i.d. (COINJECTED) (#FLINCHES)
FORMALIN 2.5%

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FORMALIN 2.5%

RAT # \ BIN	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	AUC 0-12	AUC 16-36	AUC 40-60	AUC 16-60	AUC 0-60
9714.01	5	16	6	20	11	7	22	22	22	9	22	34	30	15	10	27	104	120	224	251
9714.04	18	6	4	6	8	23	16	26	30	15	26	12	21	9	9	28	109	94	203	231
9714.05	23	23	3	8	15	17	26	34	30	26	33	18	19	13	9	49	130	118	248	297
9714.08	4	0	2	0	17	15	23	42	18	46	30	36	8	17	3	6	115	140	255	261
9714.09	14	8	0	2	22	21	11	16	37	17	21	18	9	5	4	22	109	74	183	205
9714.12	10	0	0	0	9	21	25	12	24	31	9	19	20	22	21	10	91	122	213	223
MEAN	12.3	8.8	2.5	6.0	13.7	17.3	20.5	25.3	26.8	24.0	23.8	22.8	17.8	13.5	9.3	23.7	109.7	111.3	221.0	244.7
N	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0
SD	7.4	9.1	2.3	7.6	5.4	5.9	5.8	11.2	6.8	13.4	8.6	9.8	8.2	6.0	6.4	15.3	12.8	23.4	27.3	32.5
SE	3.0	3.7	1.0	3.1	2.2	2.4	2.4	4.6	2.8	5.5	3.5	4.0	3.4	2.4	2.6	6.3	5.2	9.6	11.1	13.3

FORMALIN 2.5% + AMITRIPTYLINE 100nmol (COINJECTED)

RAT # \ BIN	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	AUC 0-12	AUC 16-36	AUC 40-60	AUC 16-60	AUC 0-60
9714.02	0	0	0	0	0	0	0	4	2	3	1	3	4	1	2	0	6	14	20	20
9714.03	0	0	0	0	0	0	8	18	5	4	25	13	11	8	8	0	31	69	100	100
9714.06	0	0	0	0	1	0	3	7	2	0	2	8	11	4	2	0	13	27	40	40
9714.07	0	0	2	1	0	1	6	2	2	6	4	1	4	3	1	2	12	19	31	33
9714.10	0	0	0	0	0	0	0	0	0	8	2	12	4	6	0	0	0	32	32	32
9714.11	0	0	0	0	5	4	5	8	22	12	6	13	9	6	9	0	44	55	99	99
MEAN	0.0	0.0	0.3	0.2	1.0	0.8	3.7	6.5	5.5	5.5	6.7	8.3	7.2	4.7	3.7	0.3	17.7	36.0	53.7	54.0
N	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0
SD	0.0	0.0	0.8	0.4	2.0	1.6	3.3	6.4	8.2	4.2	9.2	5.3	3.5	2.5	3.8	0.8	16.6	21.5	36.1	35.8
SE	0.0	0.0	0.3	0.2	0.8	0.7	1.3	2.6	3.4	1.7	3.7	2.2	1.4	1.0	1.6	0.3	6.8	8.8	14.7	14.6

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FORMALIN 2.5% + AMITRIPTYLINE 100nmol i.d. (COINJECTED) (TIME SPENT BITING/LICKING)

FORMALIN 2.5%

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FORMALIN 2.5%

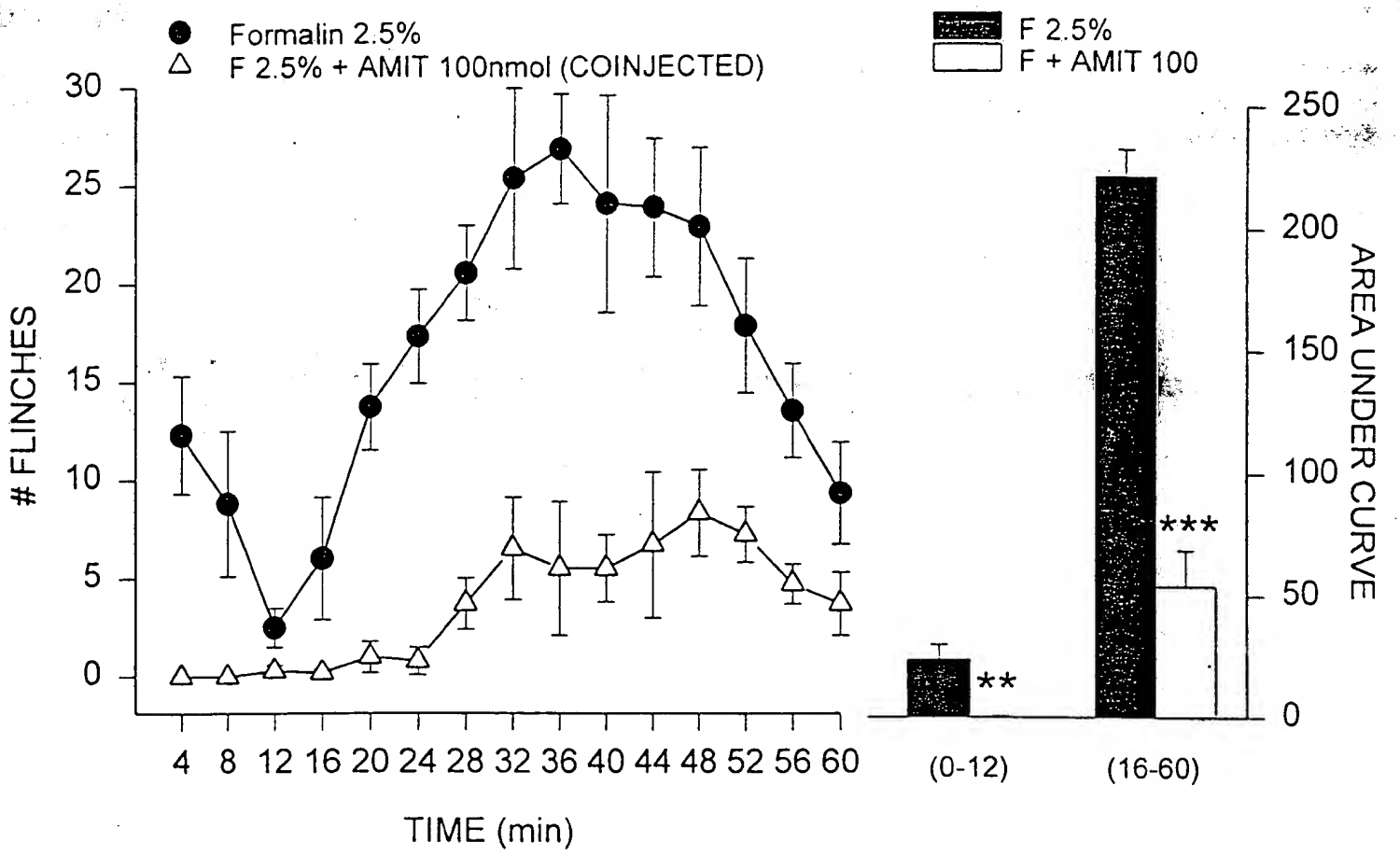
RAT # \ BIN	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	AUC 0-12	AUC 16-36	AUC 40-60	AUC 16-60	AUC 0-60
9714.01	1	0	0	0	49	78	17	81	48	71	58	13	21	5	0	1	273	168	441	442
9714.04	0	0	0	0	7	18	71	46	18	29	9	30	0	17	11	0	160	96	256	256
9714.05	17	8	0	0	55	15	53	36	34	26	11	0	61	0	0	25	193	98	291	316
9714.08	0	0	0	0	0	47	39	11	40	0	0	0	32	10	0	0	137	42	179	179
9714.09	2	0	0	0	1	15	29	47	26	26	5	0	0	0	0	2	118	31	149	151
9714.12	0	0	0	0	0	0	0	2	16	52	93	67	25	57	29	0	18	323	341	341
MEAN	3.3	1.3	0.0	0.0	18.7	28.8	34.8	37.2	30.3	34.0	29.3	18.3	23.2	14.8	6.7	4.7	149.8	126.3	276.2	280.8
N	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0
SD	6.7	3.3	0.0	0.0	26.0	26.6	25.4	28.4	12.6	24.5	37.6	26.6	22.8	21.6	11.8	10.0	84.5	108.0	107.3	108.3
SE	2.8	1.3	0.0	0.0	10.6	11.7	10.4	11.6	5.1	10.0	15.4	10.9	9.3	8.8	4.8	4.1	34.5	44.1	43.8	44.2

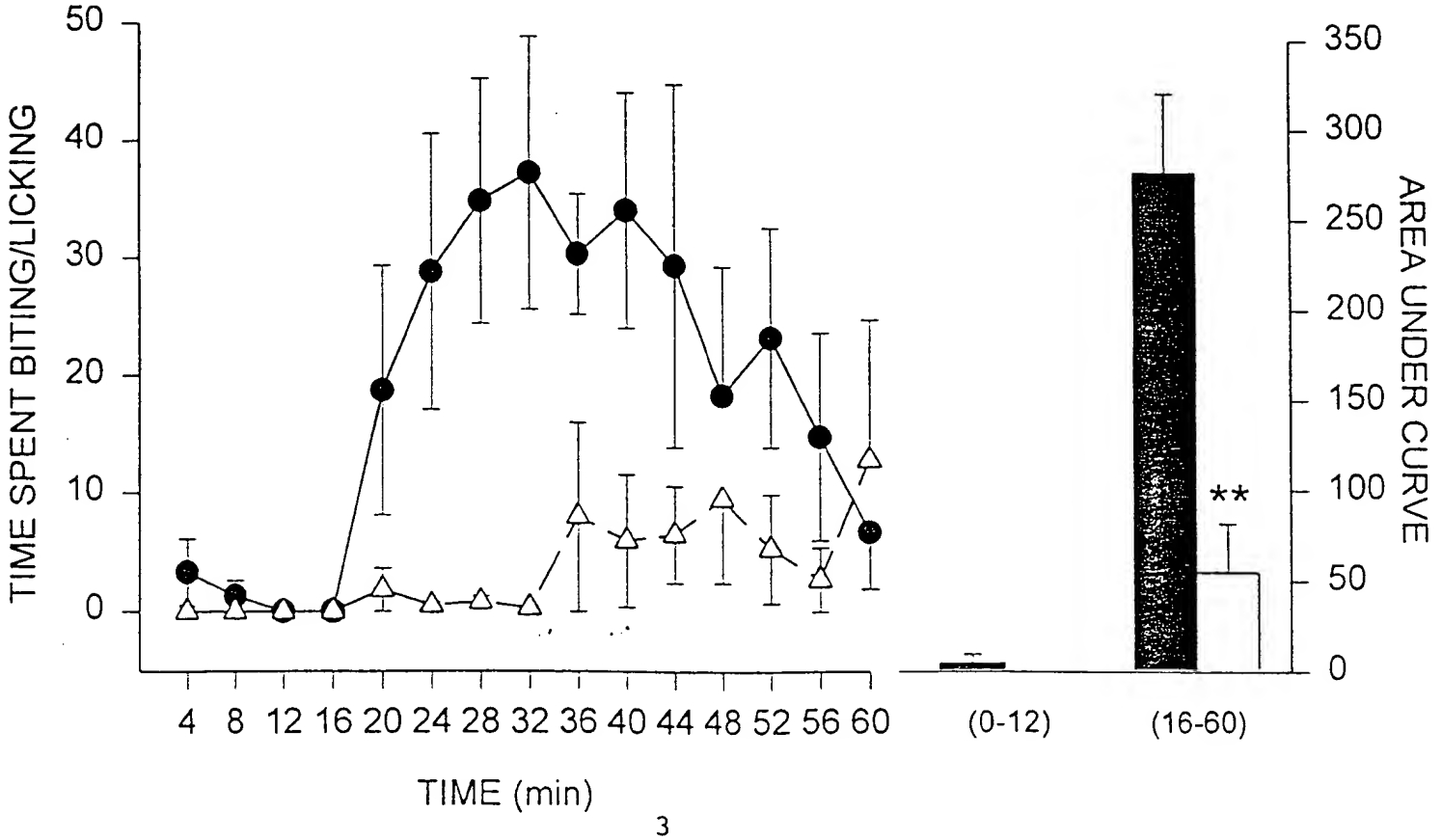
FORMALIN 2.5% + AMITRIPTYLINE 100nmol (COINJECTED)

RAT # \ BIN	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	AUC 0-12	AUC 16-36	AUC 40-60	AUC 16-60	AUC 0-60
9714.02	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
9714.03	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
9714.06	0	0	0	0	0	0	2	1	48	0	0	0	28	16	72	0	51	116	167	167
9714.07	0	0	0	0	0	2	3	1	0	34	19	14	0	0	0	0	6	67	73	73
9714.10	0	0	0	0	0	0	0	0	0	2	0	0	4	0	0	0	0	6	6	6
9714.11	0	0	0	0	11	1	0	0	0	0	20	43	0	0	5	0	12	68	80	80
MEAN	0.0	0.0	0.0	0.0	1.8	0.5	0.8	0.3	8.0	6.0	6.5	9.5	5.3	2.7	12.8	0.0	11.5	42.8	54.3	54.3
N	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0
SD	0.0	0.0	0.0	0.0	4.5	0.8	1.3	0.5	19.6	13.7	10.1	17.3	11.2	6.5	29.1	0.0	19.9	48.2	66.2	66.2
SE	0.0	0.0	0.0	0.0	1.8	0.3	0.5	0.2	8.0	5.6	4.1	7.1	4.6	2.7	11.9	0.0	8.1	19.7	27.0	27.0
																NS	<.01	NS	<.01	<.01

Group 9714-1

FORMALIN 2.5% + AMITRIPTYLINE 100nmol (COINJECTED)





ANOVA

Gp 9715-1BF (/ File:CopyRange) b42..q42~

FORMALIN 2.5% + AMITRIPTYLINE I.d. (COINJECTED) DOSE RESPONSE (#FLINCHES)

FORMALIN 2.5%

(/ File:CopyRange) b43..q43~

FORMALIN 2.5%

																AUC	AUC	AUC	AUC	AUC
RAT # \ BIN	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	0-12	16-36	40-60	16-60	0-60
9714.01	5	16	6	20	11	7	22	22	22	9	22	34	30	15	10	27	104	120	224	251
9714.04	18	6	4	6	8	23	16	26	30	15	28	12	21	9	9	28	109	94	203	231
9714.05	23	23	3	8	15	17	26	34	30	28	33	18	19	13	9	49	130	118	248	297
9714.08	4	0	2	0	17	15	23	42	18	48	30	36	8	17	3	6	115	140	255	261
9714.09	14	8	0	2	22	21	11	16	37	17	21	18	9	5	4	22	109	74	183	205
9714.12	10	0	0	0	9	21	25	12	24	31	9	19	20	22	21	10	91	122	213	223
9715.04	0	0	0	0	7	21	15	29	23	29	21	24	12	3	5	0	95	94	189	189
MEAN	10.6	7.6	2.1	5.1	12.7	17.9	19.7	25.9	26.3	24.7	23.4	23.0	17.0	12.0	8.7	20.3	107.6	108.9	216.4	236.7
N	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0
SD	8.2	9.0	2.3	7.3	5.5	5.5	5.7	10.3	6.4	12.3	7.9	8.9	7.8	6.8	6.1	16.6	13.0	22.4	27.7	36.4
SE	3.1	3.4	0.9	2.8	2.1	2.1	2.2	3.9	2.4	4.7	3.0	3.4	3.0	2.6	2.3	6.3	4.9	8.5	10.5	13.7

FORMALIN 2.5% + AMITRIPTYLINE 10nmol (COINJECTED)

																AUC	AUC	AUC	AUC	AUC
RAT # \ BIN	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	0-12	16-36	40-60	16-60	0-60
9715.12	17	3	12	27	28	34	33	40	26	35	21	37	20	30	18	32	188	161	349	381
9715.16	0	0	3	1	12	21	16	15	24	16	14	8	6	4	5	3	89	53	142	145
9715.17	0	0	0	2	10	35	11	10	28	18	11	15	7	9	0	0	96	60	156	156
9715.22	0	1	1	1	0	0	15	7	4	4	4	9	0	5	2	2	27	24	51	53
9715.23	0	0	4	2	3	7	11	3	21	23	22	18	4	7	0	4	47	74	121	125
MEAN	3.4	0.8	4.0	6.6	10.6	19.4	17.2	15.0	20.6	19.2	14.4	17.4	7.4	11.0	5.0	8.2	89.4	74.4	163.8	172.0
N	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
SD	7.6	1.3	4.7	11.4	10.9	15.7	9.1	14.6	9.6	11.3	7.4	11.7	7.5	10.8	7.5	13.4	62.2	51.7	111.1	123.5
SE	3.4	0.6	2.1	5.1	4.9	7.0	4.1	6.5	4.3	5.0	3.3	5.2	3.4	4.8	3.4	6.0	27.8	23.1	49.7	55.2
																<.05	NS	<.05	NS	NS

FORMALIN 2.5% + AMITRIPTYLINE 30nmol (COINJECTED)

																AUC	AUC	AUC	AUC	AUC
RAT # \ BIN	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	0-12	16-36	40-60	16-60	0-60
9715.13	0	1	0	7	12	10	30	24	29	27	14	8	7	11	10	1	112	77	189	190
9715.15	1	0	0	0	0	0	0	15	6	4	4	10	15	9	9	1	21	51	72	73
9715.18	0	0	0	0	0	1	4	3	6	15	5	9	2	5	1	0	14	37	51	51
9715.19	0	0	0	0	0	0	0	6	0	0	13	11	7	5	5	0	6	41	47	47
9715.21	0	2	0	1	4	2	21	28	35	12	13	11	5	9	13	2	91	63	154	156
9715.24	0	1	0	1	2	3	4	10	13	16	0	3	1	1	3	1	33	24	57	58
MEAN	0.2	0.7	0.0	1.5	3.0	2.7	9.8	14.3	14.8	12.3	8.2	8.7	6.2	6.7	6.8	0.8	46.2	48.8	95.0	95.8
N	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0
SD	0.4	0.8	0.0	2.7	4.7	3.8	12.6	10.0	14.0	9.6	5.9	3.0	5.0	3.7	4.6	0.8	44.3	19.1	60.9	61.4
SE	0.2	0.3	0.0	1.1	1.9	1.5	5.1	4.1	5.7	3.9	2.4	1.2	2.0	1.5	1.9	0.3	18.1	7.8	24.9	25.1
																<.01	<.05	<.01	<.01	<.01

FORMALIN 2.5% + AMITRIPTYLINE 100nmol (COINJECTED)

																AUC	AUC	AUC	AUC	AUC
RAT # \ BIN	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	0-12	16-36	40-60	16-60	0-60
9714.02	0	0	0	0	0	0	0	4	2	3	1	3	4	1	2	0	6	14	20	20
9714.03	0	0	0	0	0	0	8	18	5	4	25	13	11	8	8	0	31	69	100	100
9714.06	0	0	0	0	1	0	3	7	2	0	2	8	11	4	2	0	13	27	40	40
9714.07	0	0	2	1	0	1	6	2	2	6	4	1	4	3	1	2	12	19	31	33
9714.10	0	0	0	0	0	0	0	0	0	8	2	12	4	6	0	0	0	32	32	32
9714.11	0	0	0	0	5	4	5	8	22	12	6	13	9	8	9	0	44	55	99	99
9715.01	0	0	0	0	0	0	0	0	0	1	2	0	1	2	0	0	0	6	6	6
9715.05	0	0	0	1	1	8	10	11	5	15	8	16	5	6	7	0	36	57	93	93
9715.08	0	0	2	4	20	8	14	16	7	18	8	1	4	2	3	2	69	34	103	105
9715.09	0	0	0	0	0	1	5	0	10	7	3	2	4	2	4	0	16	22	38	38
9715.20	0	0	0	0	0	0	0	0	1	5	2	3	7	6	7	0	1	30	31	31
MEAN	0.0	0.0	0.4	0.5	2.5	2.0	4.8	6.0	5.1	7.0	5.7	6.5	5.8	4.2	3.9	0.4	20.7	33.2	53.9	54.3
N	11.0	11.0	11.0	11.0	11.0	11.0	11.0	11.0	11.0	11.0	11.0	11.0	11.0	11.0	11.0	11.0	11.0	11.0	11.0	11.0
SD	0.0	0.0	0.8	1.2	6.0	3.2	4.7	6.6	6.4	5.3	6.9	6.0	3.3	2.3	3.3	0.8	22.0	19.5	36.8	36.9
SE	0.0	0.0	0.2	0.4	1.8	1.0	1.4	2.0	1.9	1.6	2.1	1.8	1.0	0.7	1.0	0.2	6.6	5.9	11.1	11.1
																<.01	<.001	<.001	<.001	<.001
																F=6.83 <.01	F=10.2 <.001	F=11.3 <.001	F=12.2 <.001	F=13.0 <.001

Gp 9715-1BB (/ File;CopyRange)b42..q42~

FORMALIN 2.5% + AMITRIPTYLINE i.d. (COINJECTED) DOSE RESPONSE (TIME SPENT BITING/LICKING)

FORMALIN 2.5%

(/ File;CopyRange)b43..q43~

FORMALIN 2.5%

RAT # \ BIN	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	AUC 0-12	AUC 16-36	AUC 40-60	AUC 16-60	AUC 0-60
9714.01	1	0	0	0	49	78	17	81	48	71	58	13	21	5	0	1	273	168	441	442
9714.04	0	0	0	0	7	16	71	46	18	29	9	30	0	17	11	0	160	96	256	256
9714.05	17	8	0	0	55	15	53	36	34	26	11	0	61	0	0	25	193	98	291	316
9714.08	0	0	0	0	0	47	39	11	40	0	0	0	32	10	0	0	137	42	179	179
9714.09	2	0	0	0	1	15	29	47	26	26	5	0	0	0	0	2	118	31	149	151
9714.12	0	0	0	0	0	0	0	2	16	52	93	67	25	57	29	0	18	323	341	341
9715.04	0	0	0	0	0	0	20	50	55	5	59	0	0	0	0	0	125	64	189	189
MEAN	2.9	1.1	0.0	0.0	16.0	24.7	32.7	39.0	33.9	29.9	33.6	15.7	19.9	12.7	5.7	4.0	146.3	117.4	263.7	267.7
N	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0
SD	6.3	3.0	0.0	0.0	24.8	28.3	23.8	26.3	14.8	24.9	36.1	25.3	22.5	20.5	11.1	9.3	77.7	101.4	103.4	104.8
SE	2.4	1.1	0.0	0.0	9.4	10.7	9.0	10.0	5.6	9.4	13.7	9.5	8.5	7.8	4.2	3.5	29.4	38.3	39.1	39.6

FORMALIN 2.5% + AMITRIPTYLINE 10nmol (COINJECTED)

RAT # \ BIN	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	AUC 0-12	AUC 16-36	AUC 40-60	AUC 16-60	AUC 0-60
9715.12	39	1	2	62	58	45	49	5	35	33	0	0	0	1	5	42	254	39	293	335
9715.16	0	0	0	0	0	10	33	45	0	0	0	0	0	0	0	0	88	0	88	88
9715.17	0	0	0	0	0	22	60	74	0	0	0	0	0	0	0	0	156	0	156	156
9715.22	0	0	0	7	0	11	29	0	16	0	1	0	6	0	1	0	63	8	71	71
9715.23	0	0	0	0	0	0	1	3	0	0	0	20	0	0	0	0	4	20	24	24
MEAN	7.8	0.2	0.4	13.8	11.6	17.6	34.4	25.4	10.2	6.6	0.2	4.0	1.2	0.2	1.2	8.4	113.0	13.4	126.4	134.8
N	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
SD	17.4	0.4	0.9	27.1	25.9	17.2	22.4	32.8	15.5	14.8	0.4	8.9	2.7	0.4	2.2	18.8	95.8	16.5	104.5	121.5
SE	7.8	0.2	0.4	12.1	11.6	7.7	10.0	14.7	6.9	6.6	0.2	4.0	1.2	0.2	1.0	8.4	42.9	7.4	46.7	54.3
																NS	NS	$<.05$	$<.01$	$<.01$

FORMALIN 2.5% + AMITRIPTYLINE 30nmol (COINJECTED)

RAT # \ BIN	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	AUC 0-12	AUC 16-36	AUC 40-60	AUC 16-60	AUC 0-60
9715.13	0	0	0	0	0	39	30	41	0	0	0	0	0	0	0	0	110	0	110	110
9715.15	0	0	0	0	0	0	0	0	0	0	0	48	24	10	8	0	0	90	90	90
9715.18	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
9715.19	0	0	0	0	0	0	0	5	0	0	0	0	0	0	2	0	5	2	7	7
9715.21	0	0	0	0	0	11	0	0	0	20	21	0	0	5	0	0	11	46	57	57
9715.24	0	0	1	0	19	0	59	27	0	0	0	0	0	0	0	1	105	0	105	106
MEAN	0.0	0.0	0.2	0.0	3.2	8.3	14.8	12.2	0.0	3.3	3.5	8.0	4.0	2.5	1.7	0.2	38.5	23.0	61.5	61.7
N	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0
SD	0.0	0.0	0.4	0.0	7.8	15.7	24.7	17.6	0.0	8.2	8.6	19.6	9.8	4.2	3.2	0.4	53.6	37.5	48.6	48.8
SE	0.0	0.0	0.2	0.0	3.2	6.4	10.1	7.2	0.0	3.3	3.5	8.0	4.0	1.7	1.3	0.2	21.9	15.3	19.9	19.9
																NS	$<.05$	$<.05$	$<.001$	$<.001$

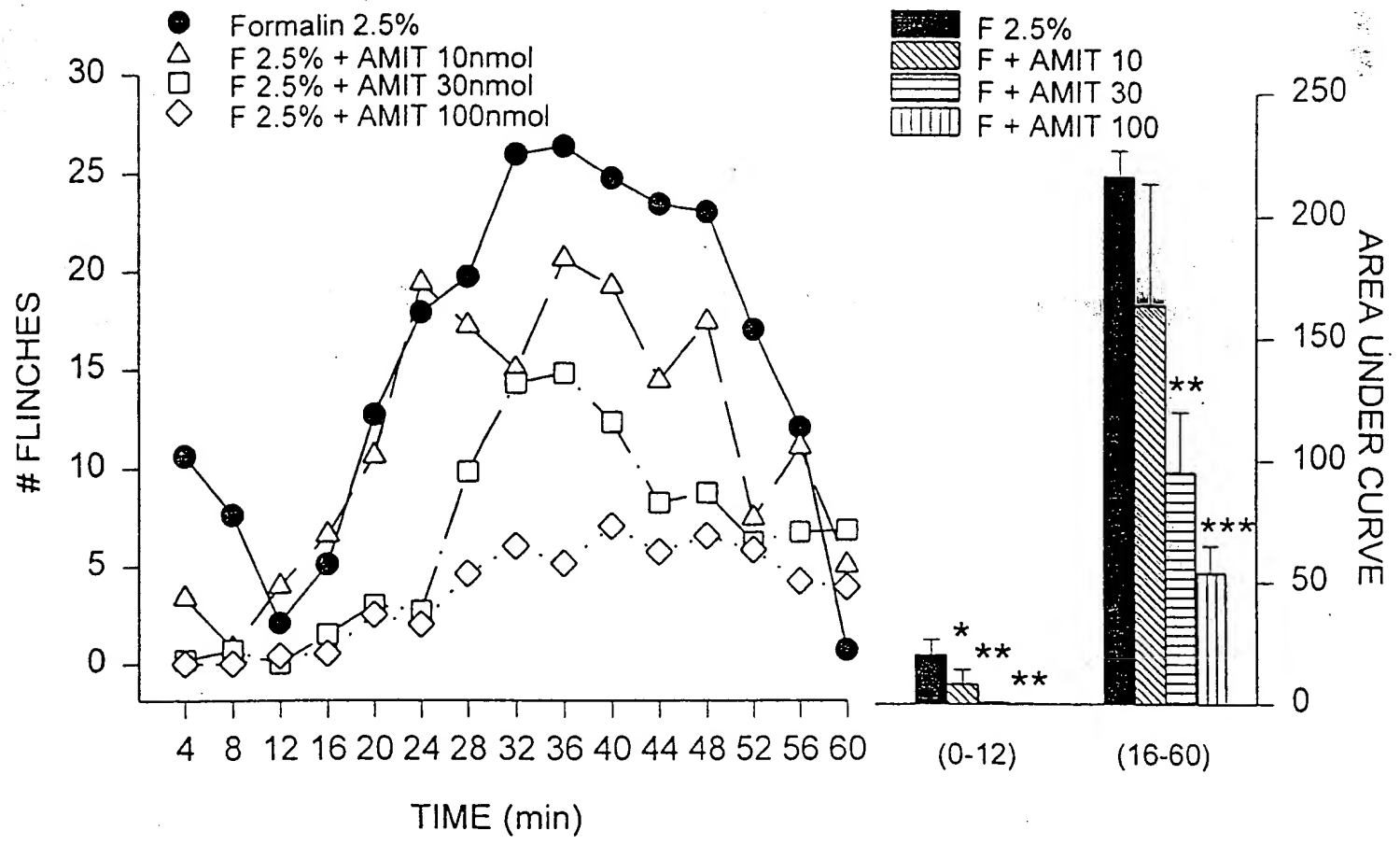
FORMALIN 2.5% + AMITRIPTYLINE 100nmol (COINJECTED)

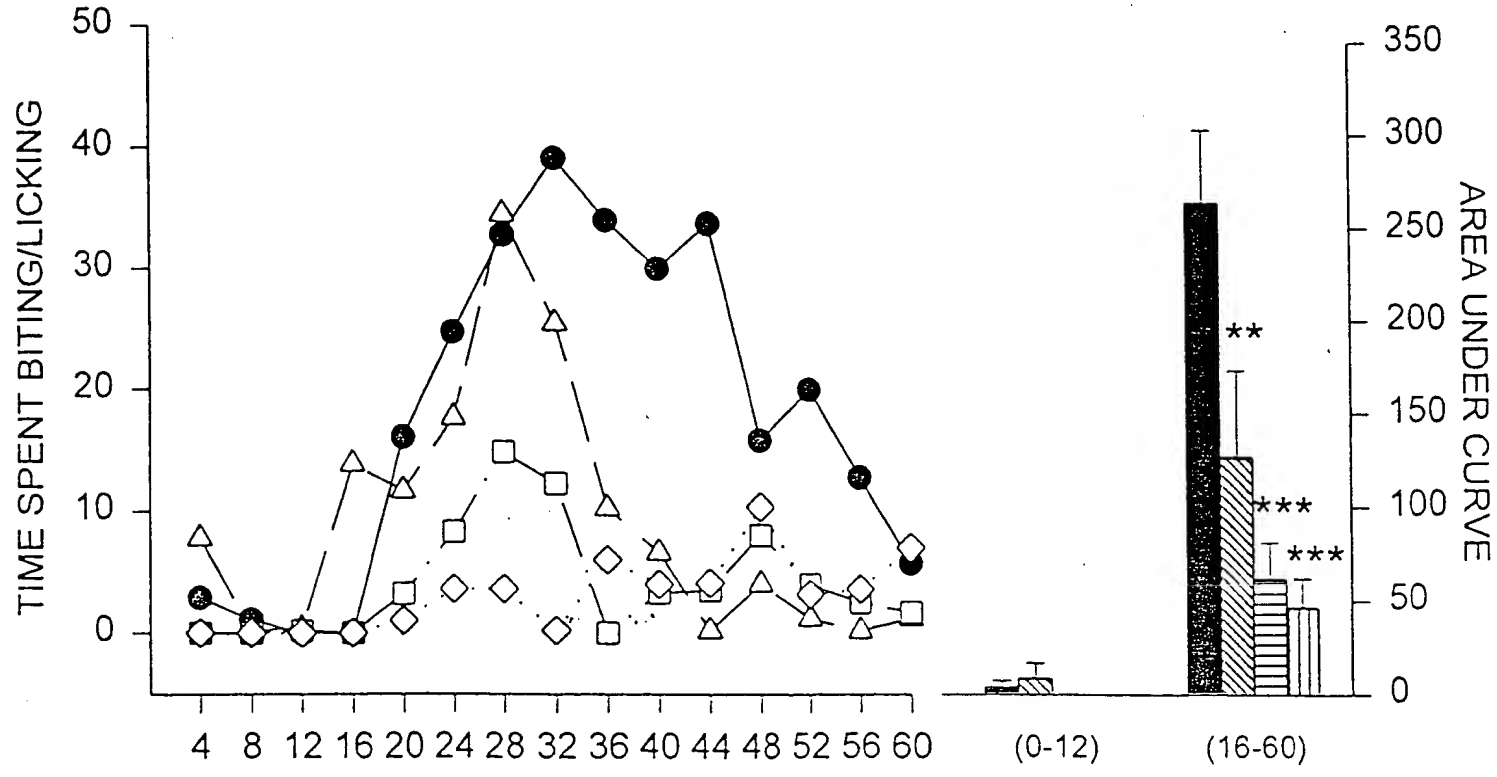
RAT # \ BIN	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	AUC 0-12	AUC 16-36	AUC 40-60	AUC 16-60	AUC 0-60
9714.02	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
9714.03	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
9714.06	0	0	0	0	0	0	2	1	48	0	0	0	28	16	72	0	51	116	167	167
9714.07	0	0	0	0	0	2	3	1	0	34	19	14	0	0	0	0	6	67	73	73
9714.10	0	0	0	0	0	0	0	0	0	2	0	0	4	0	0	0	0	6	6	6
9714.11	0	0	0	0	11	1	0	0	0	0	20	43	0	0	5	0	12	68	80	80
9715.01	0	0	0	0	0	0	0	0	0	0	0	0	0	24	0	0	0	24	24	24
9715.05	0	0	0	0	0	0	0	0	18	0	5	0	3	0	0	0	18	8	26	26
9715.08	0	0	0	0	0	37	35	0	0	0	0	0	0	0	0	0	72	0	72	72
9715.09	0	0	0	0	0	0	0	0	0	8	1	56	0	0	0	0	0	65	65	65
9715.20	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
MEAN	0.0	0.0	0.0	0.0	1.0	3.6	3.6	0.2	6.0	4.0	4.1	10.3	3.2	3.6	7.0	0.0	14.5	32.2	46.6	46.6
N	11.0	11.0	11.0	11.0	11.0	11.0	11.0	11.0	11.0	11.0	11.0	11.0	11.0	11.0	11.0	11.0	11.0	11.0	11.0	11.0
SD	0.0	0.0	0.0	0.0	3.3	11.1	10.5	0.4	14.9	10.2	7.8	20.1	8.4	8.3	21.8	0.0	24.5	40.1	51.4	51.4
SE	0.0	0.0	0.0	0.0	1.0	3.3	3.2	0.1	4.5	3.1	2.3	6.0	2.5	2.5	6.5	0.0	7.4	12.1	15.5	15.5
																NS	$<.001$	$<.01$	$<.001$	$<.001$

$F=1.02$ $F=8.02$ $F=4.49$ $F=13.8$ $F=11.9$

Group 9715-1B

FORMALIN 2.5% + AMITRIPTYLINE (COINJECTED)
DOSE RESPONSE





APPENDIX B – COMPLETE SET OF PENDING CLAIMS

26. (Amended) A composition for local administration comprising a second or third generation antidepressant, and a vehicle suitable for topical administration.

37. The composition according to claim 26 wherein the second or third generation antidepressant has a structure:

$$Ar_3(Y)\text{-}X\text{-}Ar_4(Q)$$

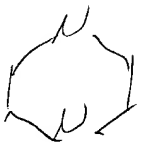
wherein Ar_3 is a substituted N-containing heterocyclic ring,

Y is either an aryl group fused to the heterocyclic ring, or one or two substituents selected from the group consisting of alkyl, alkyloxy, arylalkyl, arylalkyloxy, aryl, heteroaryl substituents, and combinations thereof comprising a total of about 4 to 8 carbons attached to Ar_3,

X is an alkyl group comprising 2 to 5 carbon atoms linking Ar_3 and Ar_4,

Ar_4 is a piperazine attached to X by a first nitrogen atom of Ar_4, and

Q is a benzene ring optionally substituted with a biocompatible halogen and attached to Ar_4 at a second nitrogen atom of Ar_4.



38. The composition according to claim 37 wherein the X is an alkyl group containing 3 carbons.

39. The composition according to claim 37 wherein Ar_3 is a 1,2,4-triazone substituted at the 4 position with the arylalkyoxy substituent containing 6 to 8 carbon atoms.

40. The composition according to claim 39 wherein the heteroarylalkyl substituent contains an oxygen atom.

41. The composition according to claim 37 wherein the benzene ring is substituted with a halogen selected from the group consisting of chlorine, bromine, and fluorine.

42. (Amended) The composition of claim 26 further comprising an inert carrier.

43. (Amended) The composition of claim 42 wherein the inert carrier is selected from the group consisting of water, isopropyl alcohol, gaseous fluorocarbons, ethyl alcohol, polyvinyl pyrrolidone, propylene glycol, a fragrance, a gel-producing material, stearyl alcohol, stearic acid, spermaceti, sorbitan monooleate, methylcellulose, and suitable combinations of any two or more thereof.

44. The composition according to claim 26 wherein the composition further comprises a penetration enhancing agent.

49. The composition according to claim 26 in a formulation selected from the group consisting of a cream, a lotion, a gel, an ointment, a spray, a powder, a polymer stabilized crystal, and an aerosol.

50. The composition of claim 26 further comprising a neutralizing agent.

51. The composition of claim 26 wherein the composition is formulated for local injection.

52. The composition according to claim 26 wherein the antidepressant is encapsulated in a slow release delivery vehicle.

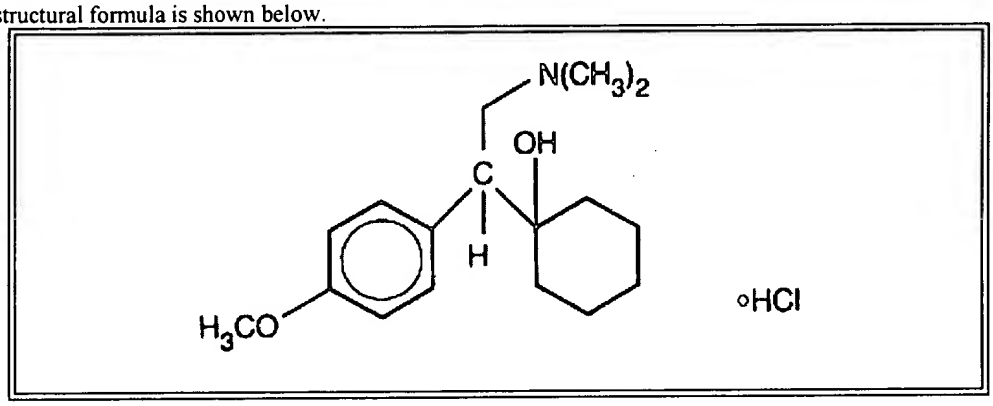
53. (Amended) The composition according to claim 52 wherein the delivery vehicle is selected from the group consisting of a liposome, a microcapsule, and a polymer stabilized crystal.

Report generated 01/24/2002 at 11:48 am

Effexor Tablets(Wyeth-Ayerst)

DESCRIPTION

Effexor (venlafaxine hydrochloride) is a structurally novel antidepressant for oral administration. It is chemically unrelated to tricyclic, tetracyclic, or other available antidepressant agents. It is designated (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride or (±)-1-[(alpha)-[(dimethylamino)methyl]-p-methoxybenzyl] cyclohexanol hydrochloride and has the empirical formula of $C_{17}H_{27}NO_2HCl$. Its weight is 313.87. The structural formula is shown below.



venlafaxine hydrochloride

Venlafaxine hydrochloride is a white to off-white crystalline solid with a solubility of 572 mg/mL in water (adjusted to ionic strength of 0.2 M with sodium chloride). Its octanol: water (0.2 M sodium chloride) partition coefficient is 0.43.

Compressed tablets contain venlafaxine hydrochloride equivalent to 25 mg, 37.5 mg, 50 mg, 75 mg, or 100 mg venlafaxine. Inactive ingredients consist of cellulose, iron oxides, lactose, magnesium stearate, and sodium starch glycolate.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of the antidepressant action of venlafaxine in humans is believed to be associated with its potentiation of neurotransmitter activity in the CNS. Preclinical studies have shown that venlafaxine and its active metabolite, O-desmethylvenlafaxine (ODV), are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. Venlafaxine and ODV have no significant affinity for muscarinic, histaminergic, or (alpha)-1 adrenergic receptors *in vitro*. Pharmacologic activity at these receptors is hypothesized to be associated with the various anticholinergic, sedative, and cardiovascular effects seen with other psychotropic drugs. Venlafaxine and ODV do not possess monoamine oxidase (MAO) inhibitory activity.

Pharmacokinetics

Venlafaxine is well absorbed and extensively metabolized in the liver. O-desmethylvenlafaxine (ODV) is the only major active metabolite. On the basis of mass balance studies, at least 92% of a single dose of venlafaxine is absorbed. Approximately 87% of a venlafaxine dose is recovered in the urine within 48 hours as either unchanged venlafaxine (5%), unconjugated ODV (29%), conjugated ODV (26%), or other minor inactive metabolites (27%). Renal elimination of venlafaxine and its metabolites is the primary route of excretion. The relative bioavailability of venlafaxine from a tablet was 100% when compared to an oral solution. Food has no significant effect on the absorption of venlafaxine or on the formation of ODV.

The degree of binding of venlafaxine to human plasma is 27%±2% at concentrations ranging from 2.5 to 2215 ng/mL. The degree of ODV binding to

human plasma is 30%±12% at concentrations ranging from 100 to 500 ng/mL. Protein-binding-induced drug interactions with venlafaxine are not expected.

Steady-state concentrations of both venlafaxine and ODV in plasma were attained within 3 days of multiple-dose therapy. Venlafaxine and ODV exhibited linear kinetics over the dose range of 75 to 450 mg total dose per day (administered on a q8h schedule). Plasma clearance, elimination half-life and steady-state volume of distribution were unaltered for both venlafaxine and ODV after multiple-dosing. Mean±SD steady-state plasma clearance of venlafaxine and ODV is 1.3±0.6 and 0.4±0.2 L/h/kg, respectively; elimination half-life is 5±2 and 11±2 hours, respectively; and steady-state volume of distribution is 7.5±3.7 L/kg and 5.7±1.8 L/kg, respectively. When equal daily doses of venlafaxine were administered as either b.i.d. or t.i.d. regimens, the drug exposure (AUC) and fluctuation in plasma levels of venlafaxine and ODV were comparable following both regimens.

Age and Gender

A pharmacokinetic analysis of 404 venlafaxine-treated patients from two studies involving both b.i.d. and t.i.d. regimens showed that dose-normalized trough plasma levels of either venlafaxine or ODV were unaltered due to age or gender differences. Dosage adjustment based upon the age or gender of a patient is generally not necessary (see " **DOSAGE AND ADMINISTRATION** ").

Liver Disease

In 9 patients with hepatic cirrhosis, the pharmacokinetic disposition of both venlafaxine and ODV was significantly altered after oral administration of venlafaxine. Venlafaxine elimination half-life was prolonged by about 30%, and clearance decreased by about 50% in cirrhotic patients compared to normal subjects. ODV elimination half-life was prolonged by about 60% and clearance decreased by about 30% in cirrhotic patients compared to normal subjects. A large degree of intersubject variability was noted. Three patients with more severe cirrhosis had a more substantial decrease in venlafaxine clearance (about 90%) compared to normal subjects.

Dosage adjustment is necessary in these patients (see " **DOSAGE AND ADMINISTRATION** ").

Renal Disease

In a renal impairment study, venlafaxine elimination half-life after oral administration was prolonged by about 50% and clearance was reduced by about 24% in renally impaired patients (GFR =10-70 mL/min), compared to normal subjects. In dialysis patients, venlafaxine elimination half-life was prolonged by about 180% and clearance was reduced by about 57% compared to normal subjects. Similarly, ODV elimination half-life was prolonged by about 40% although clearance was unchanged in patients with renal impairment (GFR =10-70 mL/min) compared to normal subjects. In dialysis patients, ODV elimination half-life was prolonged by about 142% and clearance was reduced by about 56%, compared to normal subjects. A large degree of intersubject variability was noted.

Dosage adjustment is necessary in these patients (see " **DOSAGE AND ADMINISTRATION** ").

CLINICAL TRIALS

The efficacy of Effexor (venlafaxine hydrochloride) as a treatment for depression was established in 5 placebo-controlled, short-term trials. Four of these were 6-week trials in outpatients meeting DSM-III or DSM-III-R criteria for major depression: two involving dose titration with Effexor in a range of 75 to 225 mg/day (t.i.d. schedule), the third involving fixed Effexor doses of 75, 225, and 375 mg/day (t.i.d. schedule), and the fourth involving doses of 25, 75, and 200 mg/day (b.i.d. schedule). The fifth was a 4-week study of inpatients meeting DSM-III-R criteria for major depression with melancholia whose Effexor doses were titrated in a range of 150 to 375 mg/day (t.i.d schedule). In these 5 studies, Effexor was shown to be significantly superior to placebo on at least 2 of the following 3 measures: Hamilton Depression Rating Scale (total score), Hamilton depressed mood item, and Clinical Global Impression--Severity of Illness rating. Doses from 75 to 225 mg/day were superior to placebo in outpatient studies and a mean dose of about 350 mg/day was effective in inpatients. Data from the 2 fixed-dose outpatient studies were suggestive of a dose-response relationship in the range of 75 to 225 mg/day. There was no suggestion of increased response with doses greater than 225 mg/day.

While there were no efficacy studies focusing specifically on an elderly population, elderly patients were included among the patients studied. Overall, approximately $^{2}/_{3}$ of all patients in these trials were women. Exploratory analyses for age and gender effects on outcome did not suggest any differential responsiveness on the basis of age or sex.

INDICATIONS AND USAGE

Effexor (venlafaxine hydrochloride) is indicated for the treatment of depression.

The efficacy of Effexor in the treatment of depression was established in 6-week controlled trials of outpatients whose diagnoses corresponded most closely to the DSM-III or DSM-III-R category of major depressive disorder and in a 4-week controlled trial of inpatients meeting diagnostic criteria for major depressive disorder with melancholia (see " **CLINICAL PHARMACOLOGY** ").

Wellbutrin Tablets(Glaxo Wellcome)

DESCRIPTION

WELLBUTRIN (bupropion hydrochloride), an antidepressant of the aminoketone class, is chemically unrelated to tricyclic, tetracyclic, or other known antidepressant agents. Its structure closely resembles that of diethylpropion; it is related to phenylethylamines. It is designated as (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride. The molecular weight is 276.2. The empirical formula is $C_{13}H_{18}ClNO \cdot HCl$. Bupropion hydrochloride powder is white, crystalline, and highly soluble in water. It has a bitter taste and produces the sensation of local anesthesia on the oral mucosa.

WELLBUTRIN is supplied for oral administration as 75-mg (yellow-gold) and 100-mg (red) film-coated tablets. Each tablet contains the labeled amount of bupropion hydrochloride and the inactive ingredients: 75-mg tablet--D&C Yellow No. 10 Lake, FD&C Yellow No. 6 Lake, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, polyethylene glycol, talc, and titanium dioxide; 100-mg tablet--FD&C Red No. 40 Lake, FD&C Yellow No. 6 Lake, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, polyethylene glycol, talc, and titanium dioxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics: The neurochemical mechanism of the antidepressant effect of bupropion is not known. Bupropion does not inhibit monoamine oxidase. Compared to classical tricyclic antidepressants, it is a weak blocker of the neuronal uptake of serotonin and norepinephrine; it also inhibits the neuronal re-uptake of dopamine to some extent.

Bupropion produces dose-related central nervous system (CNS) stimulant effects in animals, as evidenced by increased locomotor activity, increased rates of responding in various schedule-controlled operant behavior tasks, and, at high doses, induction of mild stereotyped behavior.

Bupropion causes convulsions in rodents and dogs at doses approximately tenfold the dose recommended as the human antidepressant dose.

Pharmacokinetics: In humans, following oral administration of WELLBUTRIN, peak plasma bupropion concentrations are usually achieved within 2 hours, followed by a biphasic decline. The average half-life of the second (postdistributional) phase is approximately 14 hours, with a range of 8 to 24 hours. Six hours after a single dose, plasma bupropion concentrations are approximately 30% of peak concentrations. Plasma bupropion concentrations are dose-proportional following single doses of 100 to 250 mg; however, it is not known if the proportionality between dose and plasma level is maintained in chronic use.

In vitro tests show that bupropion is 80% or more bound to human albumin at plasma concentrations up to 800 µmol/L (200 mcg/mL).

The absolute bioavailability of WELLBUTRIN Tablets in humans has not been determined because an intravenous formulation for human use is not available.

However, it appears likely that only a small proportion of any orally administered dose reaches the systemic circulation intact. For example, the absolute bioavailability of bupropion in animals (rats and dogs) ranges from 5% to 20%.

Metabolism: Following oral administration of 200 mg of ^{14}C-bupropion, 87% and 10% of the radioactive dose were recovered in the urine and feces, respectively. However, the fraction of the oral dose of WELLBUTRIN excreted unchanged was only 0.5%, a finding documenting the extensive metabolism of bupropion.

Several of the known metabolites of bupropion are pharmacologically active, but their potency and toxicity relative to bupropion have not been fully characterized. However, because of their longer elimination half-lives, the plasma concentrations of at least two of the known metabolites can be expected, especially in chronic use, to be very much higher than the plasma concentration of bupropion. This is of potential clinical importance because factors or conditions altering metabolic capacity (e.g., liver disease, congestive heart failure, age, concomitant medications, etc.) or elimination may be expected to influence the degree and extent of accumulation of these active metabolites.

Furthermore, bupropion has been shown to induce its own metabolism in three animal species (mice, rats, and dogs) following subchronic administration. If induction also occurs in humans, the relative contribution of bupropion and its metabolites to the clinical effects of WELLBUTRIN may be changed in chronic use.

Plasma and urinary metabolites so far identified include biotransformation products formed via reduction of the carbonyl group and/or hydroxylation of the *tert-* butyl group of bupropion. Four basic metabolites have been identified.

They are the *erythro-* and *threo-* amino alcohols of bupropion, the *erythro-* amino diol of bupropion, and hydroxybupropion.

Hydroxybupropion appears in the systemic circulation almost as rapidly as the parent drug following a single oral dose. Its peak level is three times the peak level of the parent drug; it has a half-life on the order of 24 hours; and its AUC 0 to 60 hours is about 15 times that of bupropion.

The *threo-* amino alcohol metabolite has a plasma concentration-time profile similar to that of hydroxybupropion. The *erythro-* amino alcohol and the *erythro-* amino diol metabolites generally cannot be detected in the systemic circulation following a single oral dose of the parent drug. Hydroxybupropion and the *threo-* amino alcohol metabolites have been found to be half as potent as bupropion in animal screening tests for antidepressant drugs.

In vitro findings suggest that cytochrome P450IIB6 (CYP2B6) is the principal isoenzyme involved in the formation of hydroxybupropion, while cytochrome P450 isoenzymes are not involved in the formation of the *threo-* amino alcohol metabolite.

Because bupropion is extensively metabolized, there is the potential for drug-drug interactions, particularly with those agents that are metabolized by the cytochrome P450IIB6 (CYP2B6) isoenzyme. Although bupropion is not metablized by cytochrome P450IID6 (CYP2D6), there is the potential for drug-drug interactions when bupropion is co-administered with drugs metabolized by this isoenzyme (see PRECAUTIONS: Drug Interactions).

Populations Subgroups: Factors or conditions altering metabolic capacity (e.g., liver disease, congestive heart failure [CHF], age, concomitant medications, etc.) or elimination may be expected to influence the degree and extent of accumulation of the active metabolites of bupropion. The elimination of the major metabolites of bupropion may be affected by reduced renal or hepatic function because they are moderately polar compounds and are likely to undergo further metabolism or conjugation in the liver prior to urinary excretion.

Hepatic: The effect of hepatic impairment on the pharmacokinetics of bupropion was characterized in two single-dose studies, one in patients with alcoholic liver disease and one in patients with mild to severe cirrhosis. The first study showed that the half-life of hydroxybupropion was significantly longer in 8 patients with alcoholic liver disease than in 8 healthy volunteers (32±14 hours versus 21±5 hours, respectively). Although not statistically significant, the AUCs for bupropion and hydroxybupropion were more variable and tended to be greater (by 53% to 57%) in volunteers with alcoholic liver disease. The differences in half-life for bupropion and the other metabolites in the two patient groups were minimal.

The second study showed that there were no statistically significant differences in the pharmacokinetics of bupropion and its active metabolites in 9 patients with mild to moderate hepatic cirrhosis compared to 8 healthy volunteers. There was, however, more variability observed in some of the pharmacokinetic parameters for bupropion (AUC, C_{max}, and T_{max}) and its active metabolites ($t_{1/2}$) in patients with mild to moderate hepatic cirrhosis. In addition, in patients with severe hepatic cirrhosis, the bupropion C_{max} and AUC were substantially increased (mean difference: by approximately 70% and 3-fold, respectively) and more variable when compared to values in healthy volunteers; the mean bupropion half-life was also longer (by approximately 40%). For the metabolites, the mean C_{max} was lower (by approximately 30% to 70%), the mean AUC tended to be higher (by approximately 30% to 50%), the median T_{max} was later (by approximately 20 hours), and the mean half-lives were longer (by approximately 2- to 4-fold) in patients with severe hepatic cirrhosis than in healthy volunteers (see WARNINGS , PRECAUTIONS , and DOSAGE AND ADMINISTRATION).

Renal: The effect of renal disease on the pharmacokinetics of bupropion has not been studied. The elimination of the major metabolites of bupropion may be affected by reduced renal function.

Left Ventricular Dysfunction: During a chronic dosing study in 14 depressed patients with left ventricular dysfunction, it was found that there was substantial interpatient variability (twofold to fivefold) in the trough steady-state concentrations of bupropion, hydroxybupropion, and *threo-* amino alcohol metabolites. In addition, the steady-state plasma concentrations of these metabolites were 10 to 100 times the steady-state concentrations of the parent drug.

Age: The effects of age on the pharmacokinetics of bupropion and its metabolites have not been fully characterized, but an exploration of steady-state bupropion concentrations from several depression efficacy studies involving patients dosed in a range of 300 to 750 mg/day, on a three times daily schedule, revealed no relationship between age (18 to 83 years) and plasma concentration of bupropion. A single-dose pharmacokinetic study demonstrated that the disposition of bupropion and its metabolites in elderly subjects was similar to that of younger subjects. These data suggest there is no prominent effect of age on bupropion concentration; however, another pharmacokinetic study, single and multiple dose, has suggested that the elderly are at increased risk for accumulation of bupropion and its metabolites (see PRECAUTIONS : Geriatric Use).

INDICATIONS AND USAGE

WELLBUTRIN is indicated for the treatment of depression. A physician considering WELLBUTRIN for the management of a patient's first episode of depression should be aware that the drug may cause generalized seizures in a dose-dependent manner with an approximate incidence of 0.4% (4/1000). This incidence of seizures may exceed that of other marketed antidepressants by as much as fourfold. This relative risk is only an approximate estimate because no direct comparative studies have been conducted (see WARNINGS).

The efficacy of WELLBUTRIN has been established in three placebo-controlled trials, including two of approximately 3 weeks' duration in depressed inpatients and one of approximately 6 weeks' duration in depressed outpatients. The depressive disorder of the patients studied corresponds most closely to the Major Depression category of the APA Diagnostic and Statistical Manual III.

Major Depression implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks); it should include at least four of the following eight symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigability, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and suicidal ideation or attempts.

Effectiveness of WELLBUTRIN in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use WELLBUTRIN for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

WELLBUTRIN is contraindicated in patients with a seizure disorder.

WELLBUTRIN is contraindicated in patients treated with ZYBAN® (bupropion hydrochloride) Sustained-Release Tablets, or any other medications that contain bupropion because the incidence of seizure is dose dependent.

WELLBUTRIN is also contraindicated in patients with a current or prior diagnosis of bulimia or anorexia nervosa because of a higher incidence of seizures noted in such patients treated with WELLBUTRIN.

The concurrent administration of WELLBUTRIN and a monoamine oxidase (MAO) inhibitor is contraindicated. At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with WELLBUTRIN.

WELLBUTRIN is contraindicated in patients who have shown an allergic response to bupropion or the other ingredients that make up WELLBUTRIN Tablets.

WARNINGS

Patients should be made aware that WELLBUTRIN contains the same active ingredient found in ZYBAN, used as an aid to smoking cessation treatment, and that WELLBUTRIN should not be used in combination with ZYBAN, or any other medications that contain bupropion.

Seizures: Bupropion is associated with seizures in approximately 0.4% (4/1000) of patients treated at doses up to 450 mg/day. This incidence of seizures may exceed that of other marketed antidepressants by as much as fourfold. This relative risk is only an approximate estimate because no direct comparative studies have been conducted. The estimated seizure incidence for WELLBUTRIN increases almost tenfold between 450 and 600 mg/day, which is twice the usually required daily dose (300 mg) and one and one-third the maximum recommended daily dose (450 mg). Given the wide variability among individuals and their capacity to metabolize and eliminate drugs this disproportionate increase in seizure incidence with dose incrementation calls for caution in dosing.

During the initial development, 25 among approximately 2400 patients treated with WELLBUTRIN experienced seizures. At the time of seizure, seven patients were receiving daily doses of 450 mg or below for an incidence of 0.33% (3/1000) within the recommended dose range. Twelve patients experienced seizures at 600 mg/day (2.3% incidence); six additional patients had seizures at daily doses between 600 and 900 mg (2.8% incidence).

A separate, prospective study was conducted to determine the incidence of seizure during an 8-week treatment exposure in approximately 3200 additional patients who received daily doses of up to 450 mg. Patients were permitted to continue treatment beyond 8 weeks if clinically indicated. Eight seizures occurred during the initial 8-week treatment period and five seizures were reported in patients continuing treatment beyond 8 weeks, resulting in a total seizure incidence of 0.4%.

The risk of seizure appears to be strongly associated with dose. Sudden and large increments in dose may contribute to increased risk. While many seizures occurred early in the course of treatment, some seizures did occur after several weeks at fixed dose.

The risk of seizure is also related to patient factors, clinical situations, and concomitant medications, which must be considered in selection

Zyban Sustained-Release Tablets(Glaxo Wellcome)

DESCRIPTION

ZYBAN (bupropion hydrochloride) Sustained-Release Tablets are a non-nicotine aid to smoking cessation. ZYBAN is chemically unrelated to nicotine or other agents currently used in the treatment of nicotine addiction. Initially developed and marketed as an antidepressant (WELLBUTRIN® [bupropion hydrochloride] Tablets and WELLBUTRIN SR® [bupropion hydrochloride] Sustained-Release Tablets), ZYBAN is also chemically unrelated to tricyclic, tetracyclic, selective serotonin re-uptake inhibitor, or other known antidepressant agents. Its structure closely resembles that of diethylpropion; it is related to phenylethylamines. It is (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride. The molecular weight is 276.2. The molecular formula is $C_{13}H_{18}ClNO \cdot HCl$. Bupropion hydrochloride powder is white, crystalline, and highly soluble in water. It has a bitter taste and produces the sensation of local anesthesia on the oral mucosa.

ZYBAN is supplied for oral administration as 150-mg (purple), film-coated, sustained-release tablets. Each tablet contains the labeled amount of bupropion hydrochloride and the inactive ingredients carnauba wax, cysteine hydrochloride, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80 and titanium dioxide and is printed with edible black ink. In addition, the 150-mg tablet contains FD&C Blue No. 2 Lake and FD&C Red No. 40 Lake.

CLINICAL PHARMACOLOGY

Pharmacodynamics: Bupropion is a relatively weak inhibitor of the neuronal uptake of norepinephrine, serotonin, and dopamine, and does not inhibit monoamine oxidase. The mechanism by which ZYBAN enhances the ability of patients to abstain from smoking is unknown. However, it is presumed that this action is mediated by noradrenergic and/or dopaminergic mechanisms.

Pharmacokinetics Bupropion is a racemic mixture. The pharmacologic activity and pharmacokinetics of the individual enantiomers have not been studied. Bupropion follows biphasic pharmacokinetics best described by a two-compartment model. The terminal phase has a mean half-life (±% CV) of about 21 hours (±20%), while the distribution phase has a mean half-life of 3 to 4 hours.

Absorption Bupropion has not been administered intravenously to humans; therefore, the absolute bioavailability of ZYBAN Sustained-Release Tablets in humans has not been determined. In rat and dog studies, the bioavailability of bupropion ranged from 5% to 20%.

Following oral administration of ZYBAN to healthy volunteers, peak plasma concentrations of bupropion are achieved within 3 hours. The mean peak concentration (C_{max}) values were 91 and 143 ng/mL from two single-dose (150-mg) studies. At steady state, the mean C_{max} following a 150-mg dose every 12 hours is 136 ng/mL.

In a single-dose study, food increased the C_{max} of bupropion by 11% and the extent of absorption as defined by area under the plasma concentration-time curve (AUC) by 17%. The mean time to peak concentration (t_{max}) was prolonged by 1 hour. This effect was of no clinical significance.

Distribution In vitro tests show that bupropion is 84% bound to human plasma proteins at concentrations up to 200 mcg/mL. The extent of protein binding of the hydroxybupropion metabolite is similar to that for bupropion, whereas the extent of protein binding of the threohydrobupropion metabolite is about half that seen with bupropion. The volume of distribution (V_{ss}/F) estimated from a single 150-mg dose given to 17 subjects is 1950 L (20% CV).

Metabolism Bupropion is extensively metabolized in humans. There are three active metabolites: hydroxybupropion and the amino-alcohol isomers threohydrobupropion and erythrohydrobupropion, which are formed via hydroxylation of the *tert* -butyl group of bupropion and/or reduction of the carbonyl group. Oxidation of the bupropion side chain results in the formation of a glycine conjugate of meta-chlorobenzoic acid, which is then excreted as the major urinary metabolite. The potency and toxicity of the metabolites relative to bupropion have not been fully characterized; however, it has been demonstrated in mice that hydroxybupropion is comparable in potency to bupropion, while the other metabolites are one tenth to one half as potent. This may be of clinical importance because the plasma concentrations of the metabolites are higher than those of bupropion. In vitro findings suggest that cytochrome P450IIB6 (CYP2B6) is the principal isoenzyme involved in the formation of hydroxybupropion, while cytochrome P450 isoenzymes are not involved in the formation of threohydrobupropion.